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SHORT REPORT

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Boys with unexplained West syndrome should be examined for a mutation in the Aristaless related homeobox gene, especially, when the family history is positive for mental retardation and epilepsy.

X-linked West syndrome is very rare. We report on two brothers with West syndrome and dystonia with polyalanine expansion of the Aristaless related homeobox gene (ARX).

The index patient (Fig. 1a; III-2) was the second child of non-consanguineous parents, born in 2001 at term, after an uneventful pregnancy and delivery (birth weight 3659 g, 75th percentile; length 51 cm, 75th percentile; head circumference 35 cm, 50th percentile). At the age of 3 months he developed infantile spasms and a hypsarrhythmic EEG pattern. He promptly responded to vigabatrin therapy. At 5 months a generalised dystonia, i.e. increased muscle tone with dystonic posturing of limbs, was evident. At the age of 3 years, he is able to walk a few steps with help and grasping objects is very difficult. He has no expressive speech.

The elder brother of the index patient (Fig. 1a; III-1) was born in 1996 by caesarean section because of neonatal macrosomia (birth weight 4200 g, 90th percentile; length 53 cm, 90th percentile; head circumference 38 cm, >90th percentile). At the age of 3 months he showed dystonic movements and marked truncal hypotonia. One month later he developed infantile spasms and a hypsarrhythmic EEG pattern. He did not respond to vigabatrin, but to ACTH. At the age of 8 years he is wheel-chair bound, not talking, grasping objects is not possible.

In both children metabolic tests and neuroimaging (MRI) were normal. Actually, both brothers suffer from a severe dystonia, mental impairment and rare generalised tonic-clonic seizures (the older brother), treated with valproic acid.

The family history was remarkable. In the maternal uncle (Fig. 1a; II-3, now 37 years old), spastic tetraplegia, mental retardation and epilepsy have been present since early infancy. In retrospect, the epilepsy syndrome could not be classified. MRI was not performed in this uncle, the mother or the grandmother.

From the pedigree and the clinical findings we suspected a mutation in the *ARX* gene. Following informed consent, a sequence analysis of the coding region and flanking intronic sequences of the *ARX* gene was performed. The male proband (index patient; Fig. 1a; III-2) as well as his brother and uncle were found to be hemizygous for a 21 bp GCG repeat expansion in exon 2 of the *ARX* gene c.333_334ins(GCG)7, which expands the first of four alanine tracts from normally 16 to 23 alanine residues (Fig. 1b,c). Both the mother (Fig. 11; II-2) and the maternal grandmother (Fig. 1a; I-2) were identified as heterozygous mutation carriers using an optimised fluorescence-based PCR assay.

Mutations in the *ARX* gene have been found in a broad spectrum of disorders including X-linked infantile spasms (ISSX)/West syndrome, mental retardation [2], ataxia and dystonia (Partington syndrome), syndromic and non-syndromic forms of mental retardation, myoclonic epilepsy and X-linked lissencephaly with abnormal genitalia (XLAG) [5, 6,8]. The mutation found in our Swiss family, which is not related to previously reported families, has been described before in boys with infantile spasms and normal MRI, severe mental and motor retardation [7]. In addition to Partington syndrome, dystonia was described in a few unpublished Australian and Norwegian cases [6], but

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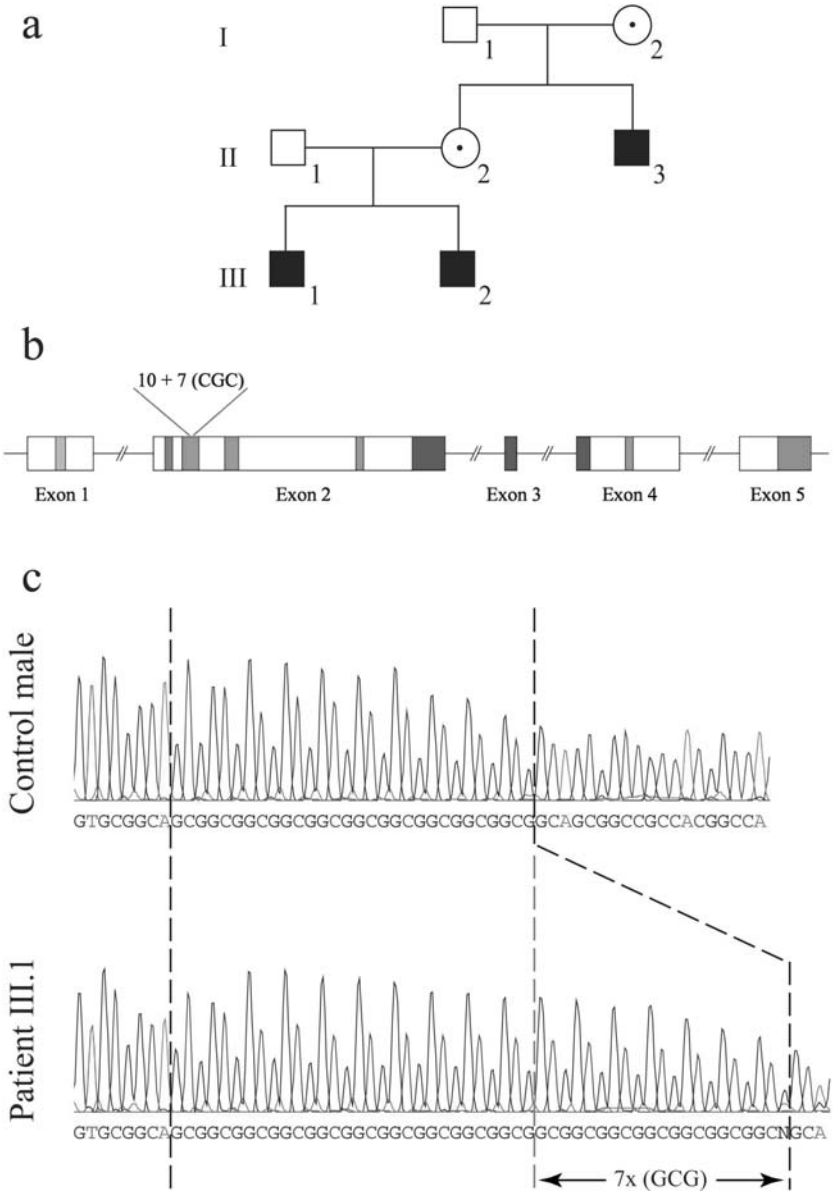

Fig. 1 **a** Family pedigree. *Black symbols* refer to patients with a hemizygous *ARX* mutation, *dotted circles* to heterozygous female carriers. **b** Schematic drawing of the *ARX* gene indicating the polyalanine domain in exon 2 (*in green*). **c** Sequencing in exon 2 of patient III.1 showing the nt333_334ins(GCG)7 with expansion of the first of four alanine tracts from 16 to 23 alanine residues

other *ARX* mutations can result in a similar phenotype [1,3]. Present observations suggest some genotype-phenotype correlation: The more severe inactivating mutations such as early truncation mutations or missense mutations in the evolutionary conserved domains cause the more severe phenotype of XLAG.

To our knowledge this is the first family presenting with typical features of X-linked West syndrome plus dystonia plus palsy resulting from expansion of the first of the four polyalanine tracts, which previously had only been associated with pure West syndrome. Critical re-evaluation of the known West syndrome families with similar mutations might reveal whether some of the affected family members indeed also present with those additional symptoms. With the identification of causal *ARX* mutations in affected families, the previously described allelic clinical entities need to be reconsidered, as many of the families like the one reported here present with an overlapping phenotype.

In mice, *ARX* is expressed in a significant proportion of neurons in the cortex, the striatum, the ganglionic eminences and also in the spinal cord. In adult mice, *ARX* expression is restricted to regions known to be rich in GABAergic neurons such as the amygdala and the olfactory bulb [4]. This could explain the occurrence of seizures in the majority of patients with an *ARX* mutation due to mislocalisation or dysfunction of GABAergic neurons. Anticonvulsant drugs increasing the neuronal GABA level, for instance valproic acid, vigabatrin, and tiagabine, might theoretically be effective in these patients.

Based on our observation and the data published by Strømme et al. [6,7] and Kato et al. [1], we conclude that *ARX* mutations should be taken into consideration in boys with otherwise unexplained West syndrome.

References

1. Kato M, Das S, Petras K, Sawaishi Y, Dobyns WB (2003) Polyalanine expansions of ARX associated with cryptogenic West syndrome. Neurology 61: 267–268
2. Mandel JL, Chelly J (2004) Monogenic X-linked mental retardation: Is it as frequent as currently estimated? The paradox of the ARX (Aristaless X) mutations. Eur J Hum Genet 12: 689–693
3. Patterson M, Zoghbi H (2003) Mental retardation: X marks the spot. Neurology 61: 156–157
4. Poirier K, Van Esch H, Friocourt G, Saillour Y, Bahi N, Backer S, Souil E, Castelnau-Ptakhine L, Beldjord C, Francis F, Bienvenu T, Chelly J (2004) Neuroanatomical distribution of ARX in brain and its localisation in GABAergic neurons. Brain Res Mol Brain Res 122: 35–46
5. Sherr EH (2003) The ARX story (epilepsy, mental retardation, autism, and cerebral malformations): one gene leads to many phenotypes. Curr Opin Pediatr 15: 567–571
6. Strømme P, Mangelsdorf ME, Scheffer IE, Gécz J (2002) Infantile spasms, dystonia, and other X-linked phenotypes caused by mutations in Aristaless related homeobox gene, ARX. Brain Dev 24: 266–268
7. Strømme P, Mangelsdorf ME, Shaw MA, Lower KM, Lewis ME, Bruyere H, Lütcherath V, Gedeon AK, Wallace RH, Scheffer IE, Turner G, Partington M, Frints SGM, Fryns JP, Sutherland GR, Mulley JC, Gécz J (2002) Mutations in the human ortholog of Aristaless cause X-linked mental retardation and epilepsy. Nat Genet 30: 441–445
8. Uyanik G, Aigner L, Martin P, Gross C, Neumann D, Marschner-Schäfer H, Hehr U, Winkler J (2003) ARX mutations in X-linked lissencephaly with abnormal genitalia. Neurology 61: 232–235